News focus

Johns Hopkins troubles raise trial questions

Following the death of a healthy volunteer in a drug trial at Johns Hopkins University, questions are once again being raised about the protocols for future studies, writes Laura Bonetta.

After a shutdown that lasted three days, human research at Johns Hopkins University has resumed under severe restrictions imposed by the US Office of Human Research Protection (OHRP). The disciplinary actions came after the death in June of an otherwise healthy volunteer who participated in an asthma study.

Meanwhile, the University of California at San Francisco (UCSF) will re-examine a 1978 study in which two research volunteers became sick after inhaling the same drug that presumably led to the death of the Johns Hopkins volunteer, 24 year old Ellen Roche. At the time of the UCSF study, lead investigators did not report the volunteers' illnesses because they did not believe they were linked to the drug. "The committee on human research is now looking at the study to see if there is anything that we can learn from it retrospectively. I do not know how long that will take," says Alice Trinkl, spokesperson for UCSF.

The drug used in both studies is hexamethonium, which blocks a class of receptors on sympathetic ganglion neurons. The drug was used as a high blood pressure medication in the 1950s and 1960s, but was taken off the market in 1972. A number of articles published in the 1950s reported that the drug could induce severe lung toxicity and even death in some patients.

Alkis Togias, lead investigator of the study at Johns Hopkins, planned to administer hexamethonium to healthy volunteers to block certain bronchial nerve ganglia and thereby investigate the neuronal mechanisms that protect the lungs of healthy individuals from asthma attacks. A university review committee that investigated the study concluded that volunteer Ellen Roche most likely died from adult respiratory distress syndrome as a result of exposure to the drug.

The committee criticised the internal review board (IRB) that approved the study for not requiring more evidence of safety in the use of hexamethonium (both Togias and the IRB apparently failed to look up the 1950s articles warning of lung damage). According to the committee's report the consent form signed by the research volunteers was 'inadequate in the description of the research risks.' In addition, committee members said that Dr. Togias should have promptly reported to the IRB that a previous volunteer in the study had

Death on trial: Johns Hopkins University is the latest center to suffer major problems in the running of a drugs trial amongst healthy volunteers. The death is leading to concerns about the procedures established to oversee the protocols for carrying out such trials

developed a cough that lasted nine days.

In the 1978 UCSF study that also used hexamethonium, one of the four volunteers complained of a headache and vague discomfort and was withdrawn from the study. Another volunteer developed chest tightness and shortness of breath after the study ended. In both cases the adverse reaction was not attributed to hexamethonium use and was not reported to review boards or in the 1980 article published in the *American Review of Respiratory Disease*. According to Neal Cohen, vice dean for academic affairs at UCSF, "23 years ago we reported events when we were aware that they were associated with a study. Today it is the standard to report all events whether we believe they are associated with a study or not."

While federal regulators have accepted Hopkins' plans to improve safeguards and lifted the suspension of human medical research, they have required that most of the 2,500 studies that were being conducted at the institution be re-reviewed by the IRBs and then approved by the OHRP.

"Priorities have been established for re-reviews so that some studies will be back in operation sooner and others later," says Joann Rodgers, a spokesperson for Johns Hopkins University.

Johns Hopkins is the latest in a number of highly publicized cases, including Duke University and the University of Pennsylvania, that have resulted in suspensions of human medical research and raised questions about the efficacy of the existing system for monitoring the safety of research volunteers. "You cannot fix the problem by pointing fingers. It is a systems problem," says Philip Walson, director of clinical trials at Children's Hospital Medical Center of Cincinnati.

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